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Strategies for enhancing the sensitivity of plasmonic nanosensors



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Based on the localized surface plasmon resonance (LSPR) of metallic nanoparti-Summary cles, plasmonic nanosensors have emerged as a powerful tool for biosensing applications. Many detection schemes have been developed and the field is rapidly growing to incorporate new methodologies and applications. Amidst all the ongoing research efforts, one common factor remains a key driving force: continued improvement of high-sensitivity detection. Although there are many excellent reviews available that describe the general progress of LSPR-based plasmonic biosensors, there has been limited attention to strategies for improving the sensitivity of plasmonic nanosensors. Recognizing the importance of this subject, this review highlights recent progress on different strategies used for improving the sensitivity of plasmonic nanosensors. These strategies are classified into the following three categories based on their different sensing mechanisms: (1) sensing based on target-induced local refractive index changes, (2) colorimetric sensing based on LSPR coupling, and (3) amplification of detection sensitivity based on nanoparticle growth. The basic principles and cutting-edge examples are provided for each kind of strategy, collectively forming a unifying framework to view the latest attempts to improve the sensitivity of nanoplasmonic sensors. Future trends for the fabrication of improved plasmonic nanosensors are also discussed.

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Introduction

Long admired for its brilliant colour, colloidal gold is known to be a fascinating material with exceptional spectral properties. It is now well known that this brilliance is due to the localized surface plasmon resonance (LSPR) of gold nanoparticles (AuNPs) [1-3]. LSPR is the collective oscillation of electrons at the surface of a nanostructure, which is excited by incident light of a larger wavelength than the size of the nanostructure. The coherent oscillation results in strong light scattering and a unique surface plasmon absorption spectrum. The intensity and peak location of the absorption and scattering spectra are highly dependent on the nanoparticle shape, size, and composition as well as the refractive index of the surrounding medium. By taking into account the relationship between the LSPR signal and its influencing factors, there has been significant interest in developing high-sensitivity chemical and biological sensors based on nanostructured platforms [3-7].

Indeed, there are many competitive advantages of LSPRbased detection strategies, as compared to other sensing modalities. The strong scattering of light derived from the LSPR of noble metal nanoparticles has enabled the optical observation of individual nanoparticles as small as 20 nm diameter for silver and 30 nm diameter for gold with darkfield microscopy [8]. Remarkably, the scattering flux of a single 80-nm silver nanosphere under the illumination of a typical white light has been reported to be equivalent to 5×10^6 fluorescein molecules or 10^5 typical quantum dots [9]. Furthermore, the LSPR of metallic nanoparticles neither blinks nor bleaches, demonstrating superiority over conventional fluorophores for long-term monitoring applications. Owing to such outstanding optical properties, metal nanostructures, particularly gold and silver, have become widely used as brightly coloured spatial labels in biological imaging [10-16], and largely replaced previous methods of fluorescence, chemiluminescence, and radioactive labelling. In addition to being used as labels, the use of plasmonic metal nanoparticles as transducers has been extensively explored in order to translate molecular binding information into changes in extinction or scattering spectra for molecular detection. As the refractive indices of organic molecules are higher than those of typical buffer solutions, the binding of organic molecules to nanoparticles increases the local refractive index, leading to a spectral redshift of the peak wavelength in both the extinction and scattering spectra [17–19]. Unlike the propagating SPR derived from a thin noble metal film which exhibits a long sensing distance (in microns) [20], the effective sensing zone of LSPR nanosensors is highly localized (within tens of nanometres) because the LSPR decays exponentially with the distance from the nanoparticle surface [21–25]. Hence, the spectral response of LSPR is sensitive only to regions within the nanoscale environment surrounding metallic nanoparticles. This highly localized sensing volume is well suited for the real-time monitoring of local refractive index changes induced by biomolecular binding events close to the nanoparticle surface [26-29].

Aside from the spectral properties of individual plasmonic nanoparticles, additional enhancements can arise from the interactions between nanoparticles. When two plasmonic nanoparticles come within close proximity to one

another (e.g., the interparticle gap is smaller than 2.5 times the length of the nanoparticle short axis) [30], the electromagnetic fields derived from the surface plasmon of individual nanoparticles may be affected by the dipolar interaction of neighbouring particles, resulting in significant changes in both the plasmon resonance extinction and scattering spectra. This near-field-coupling-induced peak shift is highly dependent on the interparticle distance. As the interparticle gap becomes smaller, larger coupling will be achieved; the coupling decays exponentially with an increasing interparticle gap [31-34]. Based on this principle, diverse chemical and biological sensors have been developed [35-37], including sensors built on the target-guided aggregation of nanoparticles, which induces a redshift in the plasmon extinction band, and sensors utilizing the dissociation of pre-aggregates of nanoparticles in the presence of target, which induces a blueshift [38].

In addition to the direct utility of a plasmon spectrum for sensing applications, optical spectroscopy of molecules in the proximity of enhanced electromagnetic fields can be used for molecular detection. As early as the 1970s, researchers reported that the Raman signal of pyridine adsorbed on a rough silver electrode increased by as much as one million-fold compared to the same molecule in solution, which is the earliest description of surfaceenhanced Raman scattering (SERS) [39-41]. This finding soon attracted widespread interest in the research community because the Raman signal obtained from a unique vibrational energy level of a molecule has very high specificity for molecular identification. However, conventional Raman scattering is very weak, and only high concentration of molecules can be detected, seriously limiting the application of this technique before the discovery of SERS. Raman signals highly enhanced by plasmonic nanostructures have enabled revolutionary advances for Raman spectroscopy, offering renewed opportunities for a wide range of applications. A recent development in SERS revealed that a signal improvement of more than 10⁶-fold can be achieved for an ensemble of molecules [42,43], and an enhancement factor of $\sim 10^{15}$ can be achieved for a single molecule, thereby enabling the use of this technique for single molecule detection [44-49]. Surface-enhanced spectroscopy has not only been applied to Raman scattering but also to fluorescence, second harmonic generation, and infrared absorption spectroscopies. These techniques are now known as surface-enhanced hyper-Raman spectroscopy (SEHRS) [50-52], surface-enhanced fluorescence (SEF) [53-55], surface-enhanced infrared absorption spectroscopy (SEIRAS) [56-60], and surface-enhanced second harmonic generation (SESHG) [61-65]. Based on these findings, a novel branch of spectroscopy, called surfaceenhanced spectroscopy (SES), has been established and continues to evolve rapidly.

In the past few years, many review articles on LSPR nanosensors have been published [1-4,7,26,66-72]. These review articles comprehensively discuss the historical development, fundamental mechanism, sensing strategies, and applications of nanosensors made of plasmonic nanostructures. However, limited attention has been paid to the various strategies used for enhancing the sensitivity of plasmonic nanosensors. To address this shortcoming, the purpose of this review article is to comprehensively highlight recent

Refractive Index Change



Scheme 1 Illustration of different strategies to improve the sensitivity of plasmonic nanosensors. There are several kinds of methods available to influence the local dielectric properties surrounding plasmonic nanoparticles that are motivated by factors such as nanoparticle characteristics, amplification schemes, and plasmon coupling.

Wavelength

advances in improving the sensitivity of plasmonic nanosensors and to summarize the different strategies used for the enhancement of the molecular detection sensitivity of peak-shift-based plasmonic nanosensors. Recent developments in this field are categorized by the different sensing strategies (Scheme 1): (1) refractive index nanosensors, (2) colorimetric sensing based on plasmon coupling, and (3) amplified sensitivity based on nanoparticle growth. In general, refractive-index-based plasmonic nanosensors have lower sensitivity than the other two approaches but possess better universality for miniaturization and multiplexing. Sensors based on plasmonic coupling can achieve moderate sensitivity with the outstanding advantage of instrumentfree detection, making them suitable for point-of-care testing. Although the detection process is rather slow because the additional growth of nanoparticles is necessary, sensors based on the secondary growth of nanoparticles can achieve the best sensitivity with a limit of detection down to the zeptomole range; hence, these sensors can be used for the monitoring of rare biomarkers at ultralow concentrations. With each of these strategies having important merits, research developments in the field are far-ranging and occur rapidly. Hence, there may be some new developments already taking place beyond the scope of this review. With this reservation, we review the latest progress with regard to the sensitivity improvement of plasmonic nanosensors and provide a framework to understand both current and future developments in the field.

Strategies for improving the sensitivity of refractive-index-based plasmonic nanosensors

Effect of nanoparticle composition, size and shape on plasmonic nanosensors

Theoretically, the LSPR can be excited in any semiconductor, metal, or alloy that has a small imaginary dielectric constant and a large negative real dielectric constant [7,73-77]. While plasmonic nanosensors are almost exclusively made of gold or silver, LSPR sensing applications of other metal and/or metal oxide nanocomposites, e.g., zinc oxide [78-80], aluminium [81-87] and copper [88-96], have also been investigated. However, the non-noble metals are susceptible to corrosion in aqueous environments and oxidation in air, both of which significantly diminish refractive index sensitivity [4]. Similarly, despite the superior sensitivity of silver, its high reactivity makes it less popular for sensing molecules in complex biological samples [98,99].

The spectral sensitivity of plasmonic nanoparticles is highly dependent on their size and geometrical parameters. Early plasmonic nanosensors were often composed of spherical or guasi-spherical nanoparticles. Recently, theoretical simulations and experimental data have demonstrated that anisotropic nanostructures exhibit higher refractive index sensitivity than spherical nanoparticles [13,97,100]. Gold nanorods have become the most popular alternative to nanospheres due to relatively mature synthesis approaches and high yields compared with other types of non-spherical nanoparticles [101]. The refractive index sensitivity of gold nanorods is typically ~250 nm per refractive index unit, whereas the refractive index sensitivity is \sim 60 nm per refractive index unit for spherical nanostructures [101-105]. Additionally, the refractive index sensitivity of gold nanorods is linearly proportional to the aspect ratio, facilitating its tunability [97]. Nanostructures of other shapes, including nanocubes [106–109], nanoshells [110-112], nanodiscs [113-115], nanotriangles [116,117], nanostars [118–120], nanobipyramids [121,122], nanorice [123,124], nanoholes [125,126], and nanocrescents [56,127–130], have also been investigated and expanded to nanocubes and nanocuboids enclosed with concave surfaces (Fig. 1).

On the other hand, practical sensing resolution depends on the absolute magnitude of the plasmon intensity. Therefore, plasmonic nanostructures with intense absorption or scattering cross-sections are favourable in their use as sensors. El-Sayed and co-workers [100] showed that the magnitude of extinction as well as the relative contribution of scattering to the extinction rapidly increase with the increasing size of gold nanospheres. Therefore, for a modality requiring a high absorption cross-section, the plasmonic nanoparticles with relatively small size (e.g. \sim 40 nm) are preferred and for a modality requiring a dominant scattering character, the nanoparticles with relatively big size (e.g. \sim 80 nm) are preferred. It is worth noting that a large plasmonic particle tends to induce a peak broadening of plasmon resonance, which plays a negative role in a sensing resolution. More information about the effects of nanoparticle size and shape on LSPR sensitivity can be found in the recent reviews [13,71].



Figure 1 Different-shaped nanostructures used for plasmonic nanosensors: (a) silver nanocubes, (b) gold nanorods, (c) gold nanooctahedrons, (d) gold nanotriangles, (e) silver nanoshells, (f) gold nanodisks, (g) hematite—gold core—shell nanorice, (h) concave gold nanocuboids, (i) gold nanocrescents, and (j) branched crystalline gold nanostructures. Reprinted from refs [109,112,113,116,123,127,131–133] with permission.

Molecular mass of targets

Initially, plasmonic nanosensors were mainly used for sensing bulk refractive index changes in the surrounding environment. Significant attention has now shifted to sensing local refractive index changes induced by biomolecular binding events because a spectral shift is generated mainly by the refractive index change at the surface of the nanoparticles (a nanometre-scale regime). A total spectral shift is dependent on the extent of the surface coverage and the thickness of the adsorbed organic layer as well as the corresponding optical properties of the adsorbate. Given the same number of molecules bound to the nanoparticle surface, a larger molecule of equivalent refractive index generates a greater surface coverage and a thicker organic layer, thus inducing greater spectral shifts. Therefore, biomolecules with relatively large molecular weight can generate higher sensitivity than small molecules, leading to the development of strategies that increase the mass of target analytes.

The first strategy involves the use of a sandwich format that consists of a primary antibody-antigen-secondary antibody conjugate (Fig. 2a) [134]. In this assay format, the primary antibody is used to capture a target and the secondary antibody is used to augment the molecular mass of the target. Subsequently, a follow-up study using an aptamer, a small nucleic acid, to replace the primary capture antibody was reported (Fig. 2b) [135]. In this work, an increased plasmonic peak shift could be obtained because the DNA strand is generally much shorter than an antibody; thus, a target protein can be pulled to the nanoparticle surface in close proximity. The limits of detection of the sandwich-formatted aptamer sensor with and without antibody enhancement were 1.6 pM and 18.3 pM, respectively, demonstrating a more than one order of magnitude improvement of the detection limit [135]. Additionally, the introduction of an aptamer as a capture molecule provided an added advantage, i.e., the reusability of the immunosensor arising from the recyclable nature of aptamers. Van Duyne's group has also demonstrated another method to amplify the LSPR wavelength shift by using a AuNP-labelled antibody (Fig. 2c) [136]. A wavelength shift of up to 400%



Figure 2 Amplification of LSPR peak shift using (a) Antibody–antigen–antibody sandwich assay format, (b) Aptamer–antigen–antibody sandwich assay format, and (c) AuNP-labelled antibody.

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was observed, leading to an approximately three-order of magnitude improvement in the limit of detection. After due consideration of plasmonic coupling between AuNPs and the Ag nanoprism used in the work, we classified this approach as an example of mass amplified sensing.

Three-dimensional assembly of nanostructures

Plasmonic nanosensors have been developed for both solution- and surface-based assay formats. Surface-based LSPR sensing provides improved stability and is also



Figure 3 Outline of the fabrication procedure of (a) metalcoated three-dimensionally ordered macroporous film for refractive index sensing and (b) a gold-nanoparticle-infiltrated polystyrene film and an experimental cell. Reprinted from refs. [17,148] with permission.

compatible with constructing array platforms for rapid and multiplex diagnostics. Whereas surface-based plasmonic nanosensors are often constructed using two-dimensionally assembled nanostructures [137-139], three-dimensional (3D) assembly of metallic nanostructures has been reported to achieve a significant improvement in the detection sensitivity of plasmonic nanosensors [140-144]. A layer-bylayer (LbL) self-assembly technique was used to fabricate a multilayered Au NP structure on guartz, leading to a four-fold improvement in the sensitivity compared with a monolayered nanosensor [145]. However, the LbL selfassembly technique typically generates a compact assembly of nanoparticles, which inherently causes serious plasmonic coupling between neighbouring nanoparticles. The coupling results in a broadened plasmonic spectrum, which is generally not preferable for improving the sensitivity of peak-shift-based plasmonic nanosensors.

To fabricate a 3D-assembled plasmonic nanostructure with a sharp plasmonic spectrum and minimized plasmonic coupling effect, a spacer is required to prevent direct contact between neighbouring nanostructures. To this end, a dipping method was developed for the fabrication of metal-coated macroporous nanostructures using silica nanospheres (Fig. 3a) [17,146,147]. The use of these fabricated materials as bulk refractive index sensors [17] and label-free



Figure 4 3D gold nanostructures fabricated using a layer-bylayer approach. (a) and (b) SEM images of a monolayer and 5-layered gold nanostructures. The scale bars are 100 nm. (c) Scheme to demonstrate a multiple –SH group modification. (d) Comparison of the 2D and 3D gold nanostructures for protein detection.

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immunosensors [146,147] was also demonstrated. Another work utilized silica nanospheres as a scaffold for the assembly of 3D metallic structures (Fig. 3b). After the immobilization of AuNPs onto the silica surface, a polystyrene film was formed between the silica spheres to anchor the AuNPs. After removal of the template with hydrofluoric acid, the obtained gold-nanoparticle-infiltrated polystyrene inverse opals exhibited an optical ''on-off switching'' capability [148].

Multiwalled carbon nanotubes (MWCNTs) have also been used as a scaffold for the construction of 3D gold nanostructures (Fig. 4) [149]. In this work, 3mercaptopropyltriethoxysilane (MPTES) was used to introduce multiple -- SH groups onto MWCNT surfaces. In contrast to the widely used aliphatic bifunctional thiols, which introduce only one -SH group to each binding site on the MWCNTs, a large number of MPTES molecules could bind to each site due to the self-polymerization properties of MPTES. Hence, a high density of Au nanoparticles could be decorated on the MWCNTs. The use of MWCNTs as a scaffold for the 3D assembly offers several advantages, including: (i) MWCNTs provide microporous structures, allowing high accessibility of target molecules to AuNPs in inner layers, and (ii) a high density of 3D-assembled AuNPs can be obtained with only a few steps because multiple layers of AuNPs can be formed on a monolayer of MWCNTs. Compared with monolayered AuNPs, the 3D structure exhibited a 20-fold higher sensitivity and a wider dynamic range for biotin/streptavidin detection (Fig. 5e).



Figure 5 (a) Schematic illustration of chromophore detection by plasmonic-molecular resonance coupling. (b) Molecular structure of the chromophore. (c) Representative LSPR spectra before (OFF) and after (ON) molecular adsorption on triangular silver nanoparticles.

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Plasmonic-molecular resonance coupling

As the refractive index sensitivity of plasmonic nanosensors is proportional to the molecular weight of analytes [7, 150], it is generally accepted that LSPR sensing techniques are not ideal for the detection of small molecules. However, the recent approach developed by Van Duyne's research group enabled LSPR-based small-molecule detection [151-153]. It was demonstrated that plasmonic-molecular resonance coupling occurs when there is appropriate spectral overlapping between the molecular absorbance and the LSPR of nanostructures [154-158]. This plasmonic-molecular resonance coupling is accompanied by a significant LSPR peak shift [151–160], allowing for the detection of small-molecularweight chromophores (Fig. 5). An LSPR peak shift of approximately 60 nm was observed when [2,3,7,8,12,13,17,18octakis(propyl)porphyrazinato]magnesium(II) was adsorbed onto triangular silver nanoparticles [152]. Thereafter, they further extended this finding for the detection of camphor [153] and rhodamine 6G [151]. Soon after, Wang and his colleagues systematically investigated the plasmonicmolecular resonance coupling between different dyes and gold nanorods and studied various influencing factors, such as the plasmonic properties of Au nanocrystals, the molecular properties of dyes, and solution pH [158,161,162]. They also reported the first direct measurement of resonance coupling between a small molecule (HITC) and a single gold nanorod [163].

In addition to the demonstration of plasmonic-molecular resonance coupling for small-molecule detection, coupling of this kind has been used for the monitoring of reversible switching of molecules from non-resonant to resonant states, so-called molecular plasmonic switching [164–170]. For instance, chemically driven redox-controllable bistable [2]rotaxane was reported for the construction of a molecular plasmonic switch (Fig. 6) [164]. The [2]rotaxane molecules bound to a gold nanodisk array switched from an oxidized state to a reduced state when exposed to a chemical oxidant and a reductant (Fig. 6a and b), yielding a plasmonic peak



Figure 6 (a) Schematic of the working principle of the redoxcontrollable bistable [2]rotaxane-based plasmonic switch. Panels (b) and (c) show the extinction spectra before and after redox switching. The initial gold nanodisk peak wavelength is 690.4 nm for (b) and 818.9 nm for (c). Reprinted from ref. [164] with permission.

shift. By contrast, no peak shift was observed during the redox cycle when the original peak wavelength of the gold nanodisk was non-resonant (Fig. 6c). Thereafter, a molecular plasmonic switch driven by photochemical and thermal stimuli was also demonstrated by Baudrion and co-workers [165]. These authors showed that when ultraviolet radiation was applied to spiropyran (SPy), a photochromic molecule, the SPy form transitioned to the merocyanine form. This transition causes the LSPR spectra of the silver nanoparticle to split into two peaks: one peak is blue-shifted and the other peak is red-shifted when compared with the original plasmon peak.

Sensing with single nanoparticles

While most plasmonic nanosensors have been constructed based on a nanoparticle cluster, there is emerging evidence that a single nanoparticle can serve as an independent sensor. Importantly, single nanoparticle plasmonic nanosensors can have a higher spatial resolution and more sensitive molecular detection limit than conventional systems based on nanoparticle ensemble. To realize the potential of plasmonic nanosensors at the single nanoparticle level, significant attention has been focused on observing submicron-scale particles with a normal optical microscope; a long lasting challenge for nanoparticles below the optical diffraction limit [171]. In this regard, darkfield microscopy has proven to be a useful technique because the scattering cross-section of a plasmonic nanoparticle under a darkfield microscope is known to be much larger than the nanoparticle's original size. For example, the average scattering radius at the 95% confidence interval of a 50-nm gold nanosphere is \sim 750 nm [116], which allows for the observation of nanoparticles under an optical microscope. Since the first single-nanoparticle-based plasmonic sensors were developed by Van Duvne's and Klar's labs around 2003 [172, 173], many studies on the theoretical and experimental



Figure 7 Scheme for a typical microscope setup for singlenanoparticle LSPR detection.

findings have been reported along with field applications of single-nanoparticle plasmonic sensors. A typical microscopic setup for a single-nanoparticle plasmonic sensor is shown in Fig. 7. Similar to a conventional darkfield microscope, the setup for a single-nanoparticle plasmonic sensor consists of a darkfield condenser, a sample stage, an objective lens, a pair of evepieces, and a colour CCD camera. Both the condenser and the objective require an oil environment to collect measurable signals from the relatively weak scattering of a single nanoparticle. In addition, a spectrometer coupled to the microscope is required to collect the LSPR spectrum of single nanoparticles. A motorized stage is preferred to replace the normal sample stage to automatically scan a user-defined area of the sample. The detailed description of the setup of such a microscope can be found in a previous publication [116].

As with plasmonic nanosensors based on a large assembly of nanoparticles, the geometry of particles has a significant effect on the figures-of-merit of single-nanoparticle plasmonic sensors. Nanoparticles with sharp edges generally exhibit high detection sensitivity, and nanorods [103,105,116,135,174-176], nanostars [118,177,178], nanoholes [179,180], and bipyramids [181–183] have all been utilized for the construction of single-nanoparticle plasmonic sensors. Chilkoti et al. [174] developed a mathematical model for the rational design of single-nanoparticle plasmonic sensors. This model was used to predict the detection figures of merit (e.g., the dynamic range and molecular detection limit) associated with various nanoparticle geometries, which were verified by an experimental study on a biotin-streptavidin binding pair. A detection limit of 27 streptavidin molecules was experimentally obtained, which is in reasonable agreement with the detection limit of 20 streptavidin molecules calculated by the mathematical model. Furthermore, single-nanoparticle plasmonic sensors have proven to be a competitive alternative for single-molecule detection. Zijlstra and co-workers [184] reported optical detection of single proteins by photothermal microscopy. The sensor consisted of a single AuNR that was functionalized with biotin at the tips of the particle. Therefore, the biotin receptors would specifically bind to the tips of AuNRs. This sensing strategy induced a sensitivity improvement of \sim 700 times over a state-of-the-art plasmon sensor [174]. Hafner et al. used gold bipyramids to construct a plasmonic sensor and explored the ultimate sensing limit of single-nanoparticle plasmonic sensors [181]. In this case, a slight plasmon peak shift of <0.5 nm was recorded when single-antigen molecules desorbed from a gold bipyramid. Ament and co-workers reported the use of a plasmonic nanosensor to monitor in real-time the desorption, adsorption, and conformational dynamics of unlabelled protein at the single-molecule level with high temporal resolution [185]. Recently, a hybrid microcavity was also demonstrated for the sensing of thyroglobulin (a tumour marker for follicular thyroid cancer) and virus MS2 (the smallest RNA marker for thyroid cancer) at the single molecule level [186,187].

A well-defined interparticle distance is vital for the fabrication of a single-nanoparticle-based detection platform. There are two principal factors to take into account. First, the interparticle distance must be sufficient to ensure that no spectral overlap occurs between neighbouring nanoparticles. Second, the nanoparticle density should be sufficient for reasonable temporal and spatial detection efficiency. We previously [105] reported a method to assemble AuNRs on a chip with controllable particle density for single-nanoparticle plasmonic nanosensor applications. The interparticle distances of gold nanorods could be controlled in the range $0.25-10\,\mu\text{m}$ by tuning the CTAB concentration, gold nanorod concentration, and incubation time (Fig. 8). A similar strategy was applied to fabricate the first microfluidic device for single-nanoparticle-based plasmonic immunosensing [103]. We demonstrated that the microfluidic chip was recyclable, and proof-of-concept of the single-nanoparticle plasmonic sensor on a chip was demonstrated for the sensitive detection of neutrophil gelatinase-associated lipocalin, a biomarker for kidney disease, with a limit of detection of 8.5 ng/mL (Fig. 9).

One of the main challenges concerning singlenanoparticle plasmonic sensing is the variation in plasmonic responses of different nanoparticles arising from the inhomogeneity of nanoparticles. The magnitude of peak shift induced by the change in local refractive index on a nanoparticle surface is linearly proportional to the LSPR peak position of a nanoparticle [116]. Therefore, nanoparticle scattering at a short LSPR peak wavelength tends to have a smaller peak shift than one at a long wavelength. As some degree of heterogeneity among any batch of nanoparticles is practically inevitable, one approach to circumventing this issue is to use the same nanoparticle for the generation of a calibration curve and for detection of analytes. This eliminates the root cause of plasmonic variation arising from the fact that more than one nanoparticle is required for the entire sensing process [176]. As illustrated in Fig. 10a, an aptamer (thrombin-specific nucleic acid) was employed as a target capture molecule due to its recyclability. This aptamer-modified plasmonic sensor exhibited high regeneration capability (Fig. 10b), and by recycling a single nanoparticle, nearly one order of magnitude of improvement in the reproducibility of biomolecular sensing was achieved compared with the data obtained from 10 different individual nanoparticles (Fig. 10c and d). This high reproducibility represents a 16-fold improvement in the limit of detection due to the improved signal-to-noise ratio [105].



Figure 8 Schematic diagram (a) and darkfield microscope images of the density-controllable fabrication of gold nanorods on a glass substrate. Reprinted from ref. [105] with permission.

Because of its high spatial resolution, a singlenanoparticle plasmonic sensor offers the potential for the development of plasmonic nanoarrays, a preferred method for high-throughput assays on biomolecules. Nanometrescaled sensing arrays may provide substantial advantages over microarrays in several respects, including a larger areal density ($\sim 10^4$ to 10^5 -fold improvement) [188,189], smaller sample volumes (thousands of times smaller) [190], and greater sensitivity (orders of magnitude higher from a copy number standpoint) [191]. Guo et al. [116] demonstrated the first proof-of-concept plasmonic nanoarray utilizing individual gold nanorods as a sensing unit (Fig. 11). Two fundamental issues associated with the utility of individual nanostructures for a plasmonic nanoarray were discussed. The first issue involved the method of tracking down the plasmonic response of respective nanostructures on substrates (Fig. 11a). A system consisting of a darkfield microscope, a motorized stage, and a spectrometer was constructed and used to establish one-to-one correspondence from the darkfield images (Fig. 11a, left), spectra library (Fig. 11a, middle), and the spectra of individual nanoparticles (Fig. 11a, right). The other fundamental issue is the variation in the LSPR signal obtained from different particles. To address this issue, an empirical formula derived from the LSPR response was proposed to normalize the recorded signal from individual nanoparticles (Fig. 11b,

left). Via the normalization process, the relative standard deviation (RSD) of the plasmonic signal from 15 nanoparticles was observed to decrease from 28.08% to 6.8%. The feasibility of the normalization formula was verified with AuNPs of three different shapes, e.g., nanorods, triangular nanoplates, and nanooctahedrons. After normalization, the RSDs of all the nanostructures were less than 10%, demonstrating the applicability of the proposed normalization approach. The proof-of-concept plasmonic nanoarray for thrombin detection is illustrated in Fig. 11c.

Characteristics of the refractive-index-based plasmonic nanosensors are compared and summarized in Table 1.

Strategies to enhance the sensitivity of sensors based on target-induced plasmon coupling

While the spectral shift of refractive-index-based plasmonic nanosensors is generated by the surrounding refractive index change caused by the adsorption of target molecules onto nanostructures, the spectral shift of plasmon-couplingbased sensors arises from target-triggered change in the interparticle distance. The factors governing the sensitivity of these two types of sensors are therefore different. Generally, the factors that affect the sensitivity of

Table 1	Advantages, disadvantages, sensitivity enhancement factors (SEF) and limit of detections (LOD) of refractive-index-based plasmonic nanosensors.					
Ref.	Target	Description	Advantage	Disadvantage	SEF	LOD
[134]	Antigen	Antibody was used to increase the molecular mass of the target.	Highly specific	High cost	100	100 fM
[136]	Antibody	Nanoparticle-antibody conjugates were used to enhance the plasmonic peak shift.	The peak shift has been increased by up to 400%.	Peak broadening	333	6.0 pM
[145]	Bulk refractive index	LbL-assembled gold nanoparticles were used as the transducer for refractive index sensor.	Simple	Plasmonic coupling between neighbouring nanoparticles	4	_
[149]	Streptavidin	MWCNTs was utilized as a scaffold for the assembly of 3D nanostructures.	Highly efficient	Relatively poor LOD	20	0.5 nM
[174]	Streptavidin	Sensing with a single gold nanorod.	An analytical model was established to predict the figures-of-merit of the sensor.	Complex analytical mode	-	18 molecules
[184]	Protein	The target molecule was bound to the tip of a single nanorod.	Single molecular detection was achieved	Variation in plasmonic response depending on the target location on the nanorod	700 (as compared with ref. [174])	1 molecule
[176]	Thrombin	Reuse a same gold nanorod for the establishment of the calibration curve and for analyte assay.	Highly reproducible	Time-consuming assay	16 as compared with conventional sensor based on single nanorods	17 pM



Figure 9 In situ assembly, regeneration, and plasmonic immunosensing of a clinical biomarker. (a) Fabrication and detection schematic diagram. (b) Darkfield images. (c) Corresponding spectra and calibration curve. Reprinted from ref. [103] with permission.

plasmon-coupling-based sensors can be organized into two categories. The first category is related to characteristics of the plasmonic nanostructures, e.g., the size, shape and composition of the nanoparticles. The other category involves external factors, e.g., the interparticle distance, the size of the aggregate (the total number of nanoparticles), and the orientation of the nanoparticles. To date, there have been extensive studies performed on the plasmon coupling of various shapes of nanostructures. However, the controlled orientation of nanoparticles in solution is extremely difficult to achieve, particularly for anisotropic nanoparticles. Therefore, most plasmon-coupling-based biosensors utilize spherical or quasi-spherical nanoparticles because these nanoparticles are non-directional. This section will emphasize the diverse schemes employed to enhance the sensitivity of plasmon-coupling-based sensors. Three of the most important enhancing factors are discussed: increased aggregate size, minimized interparticle distance, and scattering signals of plasmonic coupling.

Increased aggregate size: enzyme-guided aggregate formation

The size of aggregates during the detection process plays an important role in the intensity of the measured signals. It has been demonstrated that a measurable signal can be obtained for even relatively large interparticle distances, provided the size of aggregates is sufficiently large. For example, a significant colour change is observed from an AuNP aggregate when the individual nanoparticles are linked together by DNA strands up to 72 base-pairs (\sim 24 nm). The most common nucleic acid sensors based on the aggregation of AuNPs utilize DNA sequences with 20-30 base pair length as a linker, which corresponds to an interparticle distance of around 6-9 nm [192]. Therefore, it is possible to enhance the sensitivity of nanoparticle-aggregation-based sensors by increasing the size of aggregates. Enzymes may be a good candidate for such a purpose because of their remarkable catalytic capability, which can accelerate



Figure 10 Single-nanoparticle-based reusable plasmonic aptasensors. (a) Scheme diagram representing the reusable aptasensors. (b) Reusability of the sensor. (c) and (d) Reproducibility between randomly picked individual particles (c) and from the same particle (d).

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chemical reactions by millions-fold [193]. Analytes involved in such detection schemes include DNA, proteins and metal ions, as described below.

In recent years, enzymes have been widely applied for the development of amplified colorimetric sensors to detect DNA because the mechanisms of various enzymes involve nucleic acids as substrates [194-201]. Liu et al. developed an approach to enhance the sensitivity of a DNA sensor by using nicking endonuclease-assisted nanoparticle amplification (NEANA) [194]. This detection scheme involves a continuous strand-scission cycle, enabling the cleavage of a large molar excess of linkers. Compared to conventional fluorescent-based DNA assays, this approach offers several advantages, including ultrahigh detection sensitivity, high selectivity, and ease of handling. In addition, one of the distinct advantages of this approach is its ability to detect DNA with different strand lengths. The detection of long singlestranded DNA sequences is one of the major challenges for conventional aggregation-based colorimetric assays. However, the NEANA approach can be utilized to detect long DNA sequences that contain NEase recognition sites because the binding of linker DNA to the target sequences and enzyme-induced linker cleavage occur before nanoparticle aggregation. Yu et al. [195] reported a colorimetric assay for single-nucleotide polymorphism genotyping based on Phi29 polymerase-guided rolling circle amplification (RCA). This approach not only exhibits a high detection sensitivity of 70 fM but also does not require either a fluorescence- or radioisotope-labelled procedure in the assay. More importantly, the mutant could be identified in the presence of 10⁴-fold wild-type targets. Soon after, Liu and his colleagues combined the advantages of the RCA and the NEANA techniques in order to develop a colorimetric sensor for rapid DNA detection (Fig. 12) [196]. In particular, a highly specific padlock oligonucleotide was developed for the RCA reaction. The combination of RCA and NEANA enables the colorimetric detection of any DNA targets with high sensitivity.

In addition to DNA detection, enzyme-guided signal amplification has also been applied for the development of protein assays [202]. Yang et al. developed a colorimetric approach for highly sensitive thrombin detection based on cyclic enzymatic signal amplification (Fig. 13) [202]. In the presence of a target (thrombin), the hairpin-structured DNA probe opens due to a thrombin-aptamer interaction. The released DNA sequence is then hybridized to a linker DNA, which generates a specific DNA sequence recognizable by NEase. This process results in cleavage of the linker DNA. Note that only the linker DNA is cleaved during the reaction; the intact thrombin-aptamer can repeatedly bind to another linker DNA and lead to continuous cleaving of the linker DNA. The continuous consumption of linker DNA prevents the aggregation of AuNPs such that the solution exhibits a pink colour. However, in the absence of thrombin, no cleavage occurs, and the presence of the linker DNAs induces the aggregation of AuNPs, such that the solution exhibits a purple colour. As little as 100 nM thrombin can be distinguished by the naked eye due to enzyme-guided signal amplification. The enzyme-guided signal amplification has also been used to monitor the activity of an enzyme. For instance, a plasmon ruler was reported for the sensitive and selective determination of the activity of caspase-3 [203]. A pair of Zn_{0.4}Fe_{2.6}O₄@SiO₂@Au core-shell nanoparticles was connected by a caspase-3 cleavage sequence. In the presence of caspase-3, the linker is cleaved by caspase-3, leading to the decrease in scattering intensity of the plasmon ruler arising from increased interparticle distance. Caspase-3 activity at single molecule resolution can be detected with this method. Mirkin's group [204] designed pre-aggregated AuNPs cross-linked by DNA. In the presence of the target, deoxyribonuclease I, the DNA is cleaved at a



Figure 11 (a) One-to-one correspondence between the darkfield image, the synchronized database and the LSPR spectrum for two-dimensional (2D) nanoarrays, (b) Normalization method to minimize particle-to-particle variations in the LSPR response. (c) Proof-of-concept demonstration of a plasmonic nanoarray. Reprinted from ref. [116] with permission.

specific site such that the nanoparticle aggregates disassembles, resulting in the solution changing its colour from purple to red. Similarly, enzyme-guided signal amplification was applied to the development of activity-screening tools of endonuclease [205], kinase inhibitor [206], horseradish peroxidase [207], human telomerase [208], S1 nuclease [209], HIV-1 ribonuclease H [210], and matrix metalloproteinase-2 [211].

Enzyme-guided signal amplification has also been used for the development of a sensitive assay of metal ions and small molecules, which are often involved in enzymecatalysed reactions. For instance, a rapid colorimetric assay for the detection of Mg^{2+} was recently reported (Fig. 14) [212]. In the assay, a DNA sticky end pair and EcoRImodified nanoparticles were utilized because divalent Mg^{2+} is a cofactor to activate EcoRI cleavage of DNA. Li et al. [213] demonstrated a colorimetric aptasensor for K⁺ using nicking endonuclease. The detection mechanism is based on the competitive binding of a potassium-specific aptamer to K⁺ and a DNA linker. When the potassium-binding aptamer hybridizes with a linker, the linker strand is cleaved into



Figure 12 Scheme of the colorimetric DNA sensor based on the combination of rolling circle amplification and nickingendonuclease-assisted nanoparticle amplification. Reprinted from ref. [196] with permission.



Figure 13 Schematic illustration of the colorimetric method based on cyclic enzymatic signal amplification. Reprinted from ref. [202] with permission.



Figure 14 (a) Schematic illustration of enzyme-guided AuNP amplification for the colorimetric detection of magnesium ions. (b) Typical photo of the corresponding absorption spectra (c) of samples in the presence and absence of magnesium ions. Reprinted from ref. [212] with permission.

three fractions by the nicking endonuclease. The released aptamer can then bind to another intact linker to generate a new cycle. However, the presence of K^* can effectively prevent the hybridization between the aptamer and the linker such that the linker is not cleaved.

Minimized interparticle distance

In addition to increasing the size of aggregated nanoparticles, minimizing the interparticle distance can be an effective approach to enhance the sensitivity of



Figure 15 Schematic illustration (a) and scattering spectra (b) depicting the geometric extension of a hairpin DNA-linked AuNP dimer when SSB binds.

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plasmon-coupling-based sensors. This approach could be particularly important for the case of a nanoparticle pair, which is an essential scheme for the construction of molecular rulers and biosensors. It has been theoretically proven that plasmonic coupling between nanostructures is highly sensitive to the interparticle distance [30,35,214]. This finding was applied to monitor intermolecular interactions and also perform high-resolution imaging of the conformational change of biomolecules [215–217]. Recently, Ginger's group reported target-induced dimer formation for protein [218] and DNA [219] sensing on a single nanostructure (Fig. 15). In these studies, two nanoparticles were connected via a hairpin-structured DNA strand. Upon target binding, the hairpin loop unzips, resulting in a blueshift of the plasmonic spectrum. By contrast, the nonspecific binding of other molecules to the dimer would not unzip the DNA hairpin loop, but rather causes a refractive index increase around the particle and in turn generates a redshift in the dimer scattering resonance. This type of backward response in the scattering resonance peak shift enables sensing of the target DNA in a complex matrix such as serum, with only a relatively small spectral peak shift needed (\sim 10 nm; see Fig. 15b). More recently, a new design of the DNA linker was proposed in order to increase the magnitude of the peak shift associated with target binding (Fig. 16a) [220]. The DNA linker was designed to minimize the interparticle distance in the absence of a target such that strong LSPR coupling could be obtained. Upon target binding, the DNA hairpin loop unzips and uncouples the two nanoparticles. Thus, spectral peak shifts as large as 77 nm, corresponding to the geometrical extension of the DNA, were observed (Fig. 16b). In addition, this DNA linker is reconfigurable via simple treatment with an alkaline buffer solution.

Despite the simplicity and popularity of solution-phase homogeneous sensing using plasmonic nanoparticles, the interparticle gap of conventional solution-phase colorimetric sensors is not small enough to generate substantial LSPR peak shifts. To address this issue, large aggregates composed of thousands of nanoparticles are required to generate an observable colour change [192,221,222] (the approaches for large aggregates are presented in ''Increased aggregate size: enzyme-guided aggregate formation'' section), which is associated with at least two limitations. First,



Figure 16 (a) Schematic illustration of the plasmonic switch for target DNA sensing. (b) LSPR spectra of a typical dimer before and after target DNA binding. The dashed traces represent the LSPR spectra after regeneration of the same dimer. Reprinted from ref. [220] with permission.

the necessity of macroscopic AuNP aggregates for colour change requires a molar excess of the target molecule over AuNPs, which entails a higher concentration of the target molecule than AuNPs; otherwise no colour change can be observed. Consequently, the sensitivity of this type of sensor is relatively low. Second, the formation of large AuNP aggregates greatly reduces the dispensability of the AuNPs, which results in a relatively narrow dynamic range. To address these issues, we recently reported an oriented nanoparticle aggregation [223]. The sensing scheme is depicted in Fig. 17a. Upon target binding, the AuNPs asymmetrically functionalized with DNA probes (designated as P1 and P2)



Figure 17 (a) Schematic illustration of the oriented colorimetric biosensor. (b) and (c) represent typical extinction spectra of oriented (b) and non-oriented (c) sensors. The target concentrations for the spectra from 1 to 6 are 0, 1 pM, 10 pM, 100 pM, 1 nM and 10 nM for (b), and 0, 10 nM, 30 nM, 100 nM, 300 nM and 1000 nM for (c). Reprinted from ref. [223] with permission.

formed into a Y-shaped DNA duplex, which pulls the two linked nanoparticles to a very small separation distance (calculated to be less than 1 nm [223]). The extinction spectra of the oriented sensor exhibits a sharp peak at \sim 600 nm, indicating the formation of AuNP dimers (Fig. 17b), whereas the non-oriented version exhibits a very broad peak after target binding (Fig. 17c). The limit of detection was improved 10,000 times and the detection dynamic range was more than two orders of magnitude wider compared with the nonoriented version. Most recently, the reverse process of this sensing scheme, i.e., the disassembly of dimer, has been demonstrated for sensitive detection of environmental and food pollutes [224,225].

Scattering signals of plasmonic coupling

While plasmon-coupling-based nanosensors designed for targets in a homogeneous solution are often measured by conventional UV—vis spectrometry (or sometimes by naked eye), Storhoff and co-workers [226] discovered that the scattering signal from samples spotted on an illuminated glass slide provides greatly enhanced detection sensitivity compared with detection based on absorbance (Fig. 18). Scattering-based detection yielded a four-orders-of-magnitude improvement in the detection sensitivity, enabling the direct detection of unamplified genomic DNA

strands in zeptomole quantities. Lu et al. developed a colorimetric sensor for adenosine detection based on aptazyme-directed assembly of AuNPs [227]. It was demonstrated that colorimetric biosensors for many analytes of interest can be designed using the aptazyme-modified assembly of AuNPs, regardless of whether the analytes are directly or indirectly involved in the cleavage reaction. The colour difference could be clearly observed by the naked eye by spotting the target solution on an alumina thin-layer chromatography plate and comparing the result with data obtained using UV–visible spectroscopy. The results indicated that the observation of light scattering is a good alternative to conventional UV–vis spectroscopy analysis for nanoparticle-aggregation-based sensors.

The apparatus and techniques used for the detection of light scattering of nanoparticles immobilized on a solid substrate are different from those used for nanoparticles in a solution. Therefore, the application of the strong light scattering from aggregated nanoparticles in a solution has also been explored in addition to the solid-phase detection. According to Mie and Rayleigh's scattering theory, the light intensity scattered from a nanoparticle is proportional to R^6 (R is the radius of the nanoparticle). Thus, the detection of resonance light scattering (RLS) could be a very sensitive approach for aggregation-based plasmonic nanosensors. In fact, this detection mechanism has been



Figure 18 (a) Schematic illustration representing the ''spotand-read'' colorimetric detection method. (b) UV-visible spectra. (c) Photographs of samples on a reversed-phase plate. (d) Evanescent light-induced scatter from each sample $(1 \ \mu l)$ spotted on an illuminated glass slide.

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extensively used for the sensitive assay of DNA [228-230], proteins [231-233], small molecules [234-237] and metal ions [238-240]. The hyper-Rayleigh scattering (HRS) technique can determine the microscopic nonlinear optical properties of species in solution. The presence of a nanoparticle suspension could greatly enhance the intensity of HRS by a factor of up to 10⁵. Thus, HRS may be an ultrasensitive approach for the sensing of AuNP coupling. For example, Ray demonstrated the use of the HRS technique for the sensitive discrimination of DNA-guided AuNP assembly [228]. This approach could identify single base-pair mismatched oligonucleotides at the 10 nM level. Du and co-workers [230] expanded this HRS-based DNA detection approach to a common spectrofluorometer and observed greatly enhanced light scattering from target DNA-directed oligonucleotidefunctionalized AuNPs. A AuNP RLS-based protein assay was reported by Wang and co-workers [241]. A lysozyme-bindingaptamer was first bound to a AuNP surface via electrostatic interaction to stabilize the AuNPs at high ionic strength. In the presence of lysozyme, the DNA aptamer would bind to the lysozyme and leave the AuNP surface, resulting in the aggregation of AuNPs and enhanced plasmon RLS could be detected.

Characteristics of the target-induced plasmon-couplingbased nanosensors are compared and summarized in Table 2.



Figure 19 Signal amplification method based on nanoparticle-promoted reduction of silver (I). Reprinted from ref. [243] with permission.

Sensors based on target-guided nanoparticle growth

In addition to controllably tuning the LSPR properties of plasmonic nanoparticles based on nanoparticle characteristics (e.g., size, shape and composition), there has been interest in exploiting the scattering cross-section of spherical metal nanoparticles as this dimension is proportional to R^6 (where R is the radius of a particle), while absorption is proportional to R^3 [3]. These findings became the basis of the design of plasmonic nanosensors that employ target-guided nanoparticle growth as a sensing platform. Works in this theme can be roughly grouped into two topics: (1) chip-based scanometric detection and (2) the biocatalytic growth of AuNPs. We note that AuNPs are preferably chosen as seeds in many cases mainly because AuNPs exhibit long shelf-life stability and can relatively easily accept either a Au or Ag shell.

Scanometric array detection: AuNP serves as a label

Scanometric detection typically consists of two separate procedures. The first step involves the capture of target molecules using capture-probe-functionalized Au seeds. The second step consists of a signal amplification process, in which silver (I) is used for the enlargement of captured Au seeds. The enlarged nanoparticles are then detected with a conventional flatbed scanner. The chipbased scanometric detection approach was first reported by Mirkin and co-workers to analyze combinatorial DNA, as depicted in Fig. 19 [243]. In the presence of target DNA, oligonucleotide-modified Au seeds bind to the substrate via DNA hybridization. The substrate is then exposed to a silver growth solution to generate a silver shell around the captured Au seeds. In this detection scheme, the target molecule (i.e., DNA in this case) is not directly involved in the nanoparticle growth but instead serves to selectively capture the Au seeds present in solution and to anchor these seeds on a substrate. During the signal amplification step, a reducing agent (e.g., hydroquinone) is added to the system

Ref.	Target	Description	Advantage	Disadvantage	SEF	LOD
[194]	DNA	Nicking endonuclease-assisted amplification was introduced.	Detection of DNAs with different strand lengths	The large nanoparticle aggregates are not stable in solution.	-	0.5 fmol
[195]	DNA	Rolling circle amplification (RCA)-assisted amplification was introduced.	Detection in the presence of 10 ⁴ -fold wild types	The large nanoparticle aggregates are not stable in solution.	-	70 fM
[196]	DNA	Combination of RCA and nicking endonuclease-assisted amplification was used.	Detection with the naked eye	The large nanoparticle aggregates are not stable in solution.	10 (as compared with ref. [194])	1.0 pM
[202]	Thrombin and ATP	Cyclic enzymatic signal amplification.	Detection of proteins and small molecules.	Target molecules require an appropriate aptamers.	602 (as compared with ref. [242])	50 pM (thrombin)/100 nM (ATP)
[212]	Mg ²⁺	The detection platform is based on a combination of an EcoRI-modified nanoparticle and a double-stranded DNA with sticky ends.	Detection of pyrophosphate ion	Relatively poor sensitivity	_	0.1 μΜ
[220]	DNA	A plasmonic switch for DNA sensing is fabricated based on a pair of gold nanoparticles.	Minimized interparticle distance by a hairpin DNA	The concentration of target DNA cannot be calculated.	-	0.1 pM
[223]	DNA	Gold nanoparticles are aggregated to form dimers in the presence of a target.	Significantly improved repeatability of the sensor	The sensor can only detect DNAs.	10,000	1.0 pM
[224]	Microcystin-LR	A colorimetric sensor based on the disassembly of dimers.	Fast assay (<5 min)	Relatively poor sensitivity	-	50 pM
[226]	DNA	The sensor is based on the scattering spectrum of coupled gold nanoparticles.	Detection of unamplified genomic DNA sequences	Relatively poor reproducibility	over 10,000	333 zmol
[228]	DNA	The hyper-Rayleigh scattering (HRS) technique was used for the detection of gold nanoparticle coupling.	Detection of single base-mismatch DNA	slow hybridization process of long ss-DNA	_	10 nM

 Table 2
 Advantages, disadvantages, sensitivity enhancement factors (SEF) and limit of detections (LOD) of plasmon coupling-based nanosensors.



Figure 20 Assembly of a glucose sensor based on biocatalytic AuNP growth in the presence of glucose oxidase. Reprinted from ref. [251] with permission.

to form the silver deposition on the surface of the Au seeds, which leads to a significant LSPR peak shift. Through silverassisted signal amplification, the sensitivity of this approach was improved by two orders of magnitude compared with a fluorophore-based method.

This signal amplification scheme was soon explored for various applications, such as DNA hybridization, DNA-protein interactions, protein-protein interactions, and small molecule-protein interactions [244,245]. For instance, the combination of scanometric detection with magnetic microparticles, the so-called bio-bar-code, was demonstrated for detecting prostate-specific antigen, a cancer biomarker, with a limit of detection of 3 attomolar. The sensitivity of this method exceeds 6 orders of magnitude of clinically accepted, conventional assays [246]. The silver amplification approach was also used for monitoring carbohydrate-protein interactions, which are known to be indicators of cancer and inflammation [247-249]. For example, Liang and co-workers [248] reported a method for the highly sensitive assay of cancer-associated carbohydrate antigens. Antibody-conjugated iron oxide/gold core/shell nanocomposites were brought to an array surface by a magnetic field in order to specifically recognize carbohydrates. The sensitivity of the method reached the sub-attomole level using a combination of this detection scheme and silver enhancement. Ju and co-workers reported a silveramplified scanometric approach for the in situ investigation of carbohydrate-protein interactions on the surface of living cells [249]. A one-pot method was also developed to prepare glyconanoparticles, which can bind to concanavalin A, a mannose-specific lectin with four binding sites. Due to multivalency, significant aggregation of glyconanoparticles occurs in the presence of concanavalin A in solution. However, in the presence of cells that contain abundant mannose motifs, concanavalin A would bind to the cell surface such that the concanavalin A-induced glyconanoparticle aggregation is inhibited. Because the dispersed AuNPs tend to exhibit a higher likelihood of being enhanced by silver deposition than the aggregated AuNPs [250], the presence of mannose motif abundant cells could be easily distinguished.

Biocatalytic enlargement of AuNP: an analyte serves as a reductant or a label

Enzyme-catalyzed reactions involve the generation or consumption of reducing reagents. Because the reducing agent may reduce gold or silver ions, biocatalyzed reactions can be directly used for the enlargement of AuNPs [251–254]. Unlike scanometric detection, in the scheme of biocatalytic enlargement of AuNP, an analyte acts as a reducing agent leading to the enlargement of AuNPs. Zayats and co-workers [251] reported an approach for the fabrication of a glucose sensor utilizing H_2O_2 generated by the catalysis of glucose oxidase (GOx), as illustrated in Fig. 20. Au seeds were electrostatically immobilized on a glass substrate. Then, the AuNP-modified glass substrate was immersed into a phosphate buffer solution containing glucose, GOx, HAuCl₄ and cetyltrimethylammonium chloride (CTAC). GOx catalyzes the oxidization of glucose to gluconic acid and H_2O_2 . H_2O_2



Figure 21 Glucose detection based on catalytic gold enlargement inside a hollow silica nanoreactor. Reprinted from ref. [253] with permission.

reduces the Au ions in HAuCl₄ into gold atoms such that the AuNP seeds grow. This enlargement of AuNPs generates a significant increase of absorbance. The approach can be applied for the detection of each participating molecule in the biocatalytic reaction, i.e., glucose, GOx, or H₂O₂, separately but not in a mixture. Lim et al. [254] explored the strategy of AuNP enlargement in an alginate gel matrix for glucose sensing. AuNP seeds and glucose oxidase were coencapsulated in the alginate gel matrix. In the presence of glucose, AuNP enlargement occurs due to the GOx-catalyzed oxidation of glucose. The performance of the sensors was compared in the alginate gel matrix versus in a free solution. The results indicated that when the glucose concentration was relatively high, a redshift in absorbance was observed in the alginate matrix, indicating the growth of the AuNPs, whereas a blueshift was observed in free solution due to the formation of small AuNPs. Another enzyme associated with glucose decomposition, glucose dehydrogenase, was also explored as a glucose sensor [255]. Recently, Ha and co-workers developed a glucose sensor that can be used in a highly interfering matrix using a porous silica nanoshell (Fig. 21) [253]. The presence of a hollow nanostructure favours the penetration of small molecules but blocks large biomolecules such as DNA and proteins. Therefore, this sensor enables the selective and sensitive detection of small molecules, such as peroxide and glucose, in the presence of other components.

In addition to the direct detection of small molecules involved in enzyme-catalyzed reactions, enzyme-guided AuNP enlargement is also utilized for the sensitive detection of enzyme-labelled analytes. Rodríguez-Lorenzo and co-workers [256] developed a strategy for protein detection with inverse sensitivity (Fig. 22). Unlike most sensors that generate a signal in proportion to the concentration of targets, a sensor was developed whereby the signal was inversely proportional to the analyte concentration. As illustrated in Fig. 22b and c, at relatively low concentrations of GOX, silver ions are adsorbed and grow on silver



Figure 22 Plasmonic nanosensor with inverse sensitivity based on enzyme-guided crystal growth. (a) The detection scheme, (b) and (c). TEM images after the signal-generation step when the gold nanostars were modified with 10^{-20} g/ml GOx (b) and 10^{-14} g/ml GOx (c). (d) Calibration curve for PSA detection. Reprinted from ref. [256] with permission.

nanostars, generating a significant blueshift of the LSPR, whereas at high GOx concentrations, the nucleation of silver nanoparticles preferably occurs in solution, not on the surface of silver nanostars, generating a small peak shift. This approach enables the highly sensitive detection of the prostate-specific antigen in whole serum $(4 \times 10^{-20} \text{ M})$. Importantly, this work offers a universal approach for the detection of various proteins by labelling antibodies with an enzyme. Recently, GOx-catalyzed growth of AuNPs has been demonstrated for ultrasensitive determination of cancer biomarkers (prostate-specific antigen), and the detection sensitivity of this approach was more than 4 orders of magnitude better than that of commercial ELISA [257].

de La Rica and co-workers [258,259] combined enzymeguided AuNP enlargement with conventional ELISA for the construction of plasmonic ELISA, as illustrated in Fig. 23. Similar to conventional ELISA, a primary antibody is introduced to specifically recognize the target molecule. followed by the linkage of an enzyme-decorated streptavidin and biotinylated secondary antibodies. Although horseradish peroxidase is a frequent selection in conventional ELISA, catalase, a common enzyme found in nearly all living organisms, is used for plasmonic ELISA. In the presence of a target protein, the catalase catalyzes the decomposition of hydrogen peroxide, slowing down the enlargement of AuNPs, which results in the growth of ill-defined-morphology AuNPs, the colour of which is blue. However, in the absence of a target, the relatively high concentration of hydrogen peroxide generates rapid AuNP growth, producing quasispherical and non-aggregated AuNPs; the solution is then red in colour. The main difference between the conventional ELISA and the proposed plasmonic ELISA is the nature of the generated signals. The conventional colorimetric ELISA converts the enzyme substrate from a non-colored to a colored molecule, whereas the plasmonic ELISA turns the AuNP solution from blue to red in the presence of the analyte. The blue and red colours are easily distinguished by the naked eye, thus enabling the ultrasensitive detection of target molecules.

We note that although the glucose-GOx reaction has been predominantly utilized for AuNP growth, other enzymes, such as hydrolytic proteins, hydroxylases, and NAD(P)⁺dependent enzymes, have been employed as biocatalysts for the synthesis of metal nanoparticles [260], indicating the potential of various enzymes for the development of ultrasensitive colorimetric biosensors.

Characteristics of the target-guided gold nanoparticle growth-based nanosensors are compared and summarized in Table 3.

Conclusions and perspectives

Improving the absolute detection limit of biosensors enables the identification of substances of interest that could not be previously detected. Robust methods to achieve highly sensitive detection is critical to satisfy the growing need for powerful analytical sensor tools in various fields, e.g., diagnosis/prognosis, environmental monitoring, and food safety. Recently, gold and silver nanoparticles have been proven to be outstanding building blocks for the fabrication of all types of transducers that help to achieve this goal [261–266]. The present review summarizes the different strategies used for the enhancement of detection sensitivity of peak-shiftbased plasmonic nanosensors. Table 4 shows a brief summary and comments of these strategies.

Despite great progress having already been achieved over the past decade for improving the sensitivity of plasmonic nanosensors, many practical challenges remain before plasmonic nanosensors can reach their full potential to outperform current state-of-the-art fluorescence-, electrochemistry- and chemiluminescencebased approaches for analytical applications. Some challenges and possible trends in the near future regarding the development of plasmonic nanosensors include the following:

Pushing the detection limit – from single nanoparticle to single molecule

Currently, the techniques for single-nanoparticle detection are relatively mature. However, great challenges still remain to push the detection limit from single nanoparticle to single molecule. Although some plasmonic nanosensors have been demonstrated to exhibit single-molecule sensitivity, complicated fabrication procedures and/or the requirement of sophisticated instruments prevent their practical application. Thus, many opportunities remain to push the sensitivity of plasmonic nanosensors to single-molecule detection with relatively low cost and simple instruments.

Simplifying the detection method – from simple to no apparatus

In addition to continuous efforts to obtain an absolute low limit of detection, other trends in the development of plasmonic nanosensors include efforts to improve the simplicity of the transducers, including both the procedures used for the transducer fabrication and the sensing application. Current approaches to obtaining ultrasensitive detection often require sophisticated instruments. However, in many cases, these instruments may not be available, e.g., during outdoor environmental monitoring and/or in laboratories in resource-constrained countries. Colorimetric nanosensors that can be measured using a simple plate reader or even by the naked eye, are a good alternative to satisfy this purpose on condition that the sensitivity of current colorimetric nanosensors is greatly improved.

Miniaturization and high-throughput detection — from microarrays to nanoarrays

To eventually transfer plasmonic nanosensors from laboratory to practical applications, e.g., for clinical screening and the diagnosis of diseases in hospitals, it is vital to develop plasmonic nanosensors with the ability to perform multiplex assays. Although high-throughput techniques based on microarrays are currently available, it is envisioned that nanoarrays will play increasingly important roles in the near future. Compared with conventional microarrays, nanoarrays provide a 10^4-10^5 -fold improvement in



Figure 23 Schematic illustrating the sandwich format of the conventional ELISA and the proposed plasmonic ELISA (a) and the two possible signal generation mechanisms (b). Reprinted from ref. [258] with permission.

Table 3	3 Advantages, disadvantages, and limit of detections (LOD) of gold nanoparticle growth-based plasmonic nanosensors				
Ref.	Target	Description	Advantage	Disadvantage	LOD
[243]	DNA	Scanometric DNA array detection coupled with silver amplification was used for DNA sensing.	Highly sensitive and selective	Time-consuming	50 fM
[251]	Glucose	Enzyme-catalyzed enlargement of gold nanoparticles was used for glucose sensing.	It provides a model for other oxidase-based biosensing.	Relatively poor sensitivity	2 μΜ
[253]	Glucose	Glucose was detected by catalytic gold enlargement inside a hollow silica nanoreactor.	Selective screening of large biomolecules by hollow silica	Relatively poor sensitivity and tedious fabrication process	36 μM
[256]	Protein	The inverse sensitivity was achieved by the crystal growth either on or around the gold seed.	Inverse sensitivity	Rather tedious analytical process	40 zM
[258]	Protein	Plasmonic nanoparticles are used to realize an ELISA assay.	Detection of any proteins that can be detected with conventional ELISA	Dual-colour is not sufficient for visual quantification.	$1 imes 10^{-18} g/mL$

areal density, thousands of times less sample consumption, and greatly reduced sample diffusion time [188,267,268]. Plasmonic nanoparticles are ideal building blocks for the fabrication of nanoarrays because individual nanoparticles can serve as independent sensing units. Approaches for fabricating biomolecular nanoarrays, such as DPN [269–279] in combination with recently developed tools to track down individual nanoparticles of plasmonic nanoarrays and the method to normalize the signal discrimination could enable the generation of applicable plasmonic nanoarrays for the high-throughput detection of different types of biomolecules.

Table 4	Strategies used for enhancing the sensitivity of plasmonic nanosensors	

Category	Strategies for enhancing sensitivity	Comments
Refractive index-based sensing	Composition	Ag is superior to Au. However, the high reactivity of Ag nanoparticles must be taken into account
	Size	Small size nanoparticles have high absorption ratios, while big size nanoparticles have high scattering ratios.
	Shape	Anisotropic nanostructures exhibit higher refractive index sensitivity than spherical nanoparticles.
	Increased molecular mass	An antibody or a nanoparticle labelled antibody could effectively increase the molecular mass of a target.
	3D assembled nanostructures	3D assembly may enhance the intensity of sensing signal but the interparticle distance should be carefully controlled to avoid peak broadening.
	Plasmonic-molecular resonance coupling Sensing with single nanoparticles	An effective way to detect small-molecular-weight chromophores. Single-nanoparticle sensing greatly improve the molecular detection limit and the spatial resolution.
Sensing based on plasmon coupling	Increased aggregate size	Enzyme-amplified gold nanoparticle aggregation may increase the size of aggregates, enhancing the detection
	Minimized interparticle distance	Decreasing the interparticle distance may greatly enhance the plasmon coupling so that effectively improves the detection sensitivity
	To detect the scattering signals of plasmon coupling	The detection of scattering signal offers greatly enhanced detection sensitivity compared with detection based on absorbance.
Sensing based on nanoparticle growth	Scanometric array detection coupled with silver enhancement	The silver enhancement significantly improves the detection sensitivity.
	Biocatalytic enlargement of AuNP	Any compounds involved in the biocatalytic reaction can be detected.

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